

--13. A pharmaceutical composition, comprising a pharmaceutically-acceptable carrier and, as an active ingredient, the protein of claim 12.--

*but c5*  
--14. A purified protein capable of inducing IFN- $\gamma$  production by immunocompetent cells, wherein said protein is encoded by a DNA sequence which hybridizes to an oligonucleotide probe of SEQ ID NO:5 under the hybridization conditions of 5 x SSPE, 5 x Denhardt's solution, 0.5 w/v% SDS, 100  $\mu$ g/ml denatured salmon sperm DNA, and 45°C and after being washed with 6 x SSC.--

*B3*  
*Cont*  
--15. A pharmaceutical composition, comprising a pharmaceutically-acceptable carrier and, as an active ingredient, the protein of claim 14.--

**REMARKS**

The Office Action and the cited and applied references have been carefully reviewed. No claim is allowed. Claims 1-9 and 11-15 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

New claims 14-15, which recite hybridization conditions for hybridizing to the oligonucleotide probe of SEQ ID NO:5 as

fully supported by the specification on page 33, lines 7-13, are added. Applicants submit that no new matter is being added by these new claims.

The specification has been objected to as failing to provide proper antecedent basis for the claimed subject matter. The examiner indicated that she was unable to find the term "a pharmacological composition" for the limitations of claims 2, 6 and 9 in the specification. It should be first pointed out that claims 2, 6 and 9 recite a "pharmaceutical" composition, not a "pharmacological" composition and that there is no requirement for *ipsis verbis* support of the claim language. Nevertheless, the specification at page 3, lines 18-22, discloses:

Generally, in the case of incorporating biologically active proteins into pharmaceuticals, the developments of methods for purifying such proteins highly and effectively and those for assaying samples containing these proteins are inevitable.  
(emphasis added)

The paragraph in which the above sentence is located relates to the presently claimed protein and its incorporation into pharmaceuticals, or equivalently, pharmaceutical compositions. Accordingly, the recitation of a "pharmaceutical composition" in the claims is indeed supported by the specification.

The specification has also been objected to as using terminology, "complementary amino acid sequences", which is not generally accepted in the art and whose meaning cannot be

determined. Appropriate correction is made to page 9, line 14, to replace the erroneous term "complementary" with the term "homologous" as supported by the sentence on lines 10-13, immediately above the erroneous "complementary" term, as would be well-recognized in the art.

Reconsideration and withdrawal of the objections to the specification are therefore respectfully requested.

Claims 1-2 and 7-10 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 5,912,324 by the same inventors. This rejection is obviated by the terminal disclaimer attached hereto.

Claims 3-6 have been rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for claims limited in scope to a specific variant of said protein, which has an amino acid sequence of SEQ ID:2 where residue 70 is methionine or threonine, does not reasonably provide enablement for with claims to variants having "the amino acid sequence of SEQ ID:2 with one or more amino acid residues in SEQ ID:2 replaced with different amino acids or one or more amino acid residues deleted or added to the N-terminus of SEQ ID:2 while retaining the biological property", which, given the broadest interpretation, reads on any or all possible INF- $\gamma$  inducing proteins. This rejection is respectfully traversed.

With regard to "variants" of claim 3, applicants believe that a person of ordinary skill in the art would have been able to make the "variants" without undue experiments at the time the present invention was made based on the level of skill of the artisan and the guidance provided in the present specification. A skilled person would have been able to understand what is meant by "variants" recited in the amended claim 3 from the disclosure in the specification, for example, at page 9, third paragraph, through page 10, first paragraph, and page 15, third paragraph, through page 16, third paragraph. Based on the disclosures provided by the present specification and conventional genetic engineering techniques, a skilled person would have been able to obtain the "variants" without undue experiments. At the time the present invention was made, mutation/transformation of host cells which produce a protein were routinely and widely conducted techniques. Mutated/transformed host cells produce proteins different from the original ones in their amino acid sequences or nucleotide sequences. The protein thus produced with the mutated/transformed host cells are "variants" of the original protein. And desired "variants," such as defined in claim 3, can be easily screened out using appropriate physicochemical properties, such as the four physicochemical properties recited in claim 3, as indexes from randomly produced "variants" with general genetic engineering

techniques. This was routine work for a skilled artisan at the time the present invention was made.

In addition, applicants would like to point out that the present invention is a pioneering invention relating to a novel protein, i.e., IL-18, and therefore should not be restricted to mouse IGIF only. Applicants believe that broader claims should be given to the inventors who first made such a pioneering invention.

Claims 1, 3-6, and 8-10 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. This rejection is obviated by the cancellation of claim 10 without prejudice and by the amendments to the other rejected claims.

Claims 3, 5 and 6 have been rejected under 35 U.S.C. §102(b) as being anticipated by Nakamura et al. Nakamura is said to disclose a purified protein factor which migrates at 50-55 kDa on SDS-PAGE. The examiner indicates that compositions comprising this factor and various other substances in PBS induce the production of IFN- $\gamma$  in resting T and NK cells. The examiner states that claims 3 and 5-6 of the present invention, given the broadest interpretation, read on any or all possible INF- $\gamma$  inducing proteins with INF- $\gamma$  inducing activity as said protein is defined by its biological property, rather the particular sequence disclosed in the specification. Such broad claims include other species of proteins with the same said function, but different structural features, such as the protein factor of Nakamura. Because the

characteristic biological property of the protein factor is held to be identified in the prior art, the examiner asserts that the prior art protein inherently meets the limitations of the claims 3 and 5-6 in the instant case. This rejection is respectfully traversed.

The claim 3 as amended recites that the protein has a molecular weight of  $19,000 \pm 5,000$  daltons on gel filtration and SDS-PAGE. This is clearly different from Nakamura's molecular weight of 50-55 kDa on SDS-PAGE. Accordingly, the protein factor of Nakamura does not anticipate the presently claimed invention.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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**"VERSION WITH MARKINGS TO SHOW CHANGES MADE"**

IN THE SPECIFICATION

The paragraph beginning at page 9, line 7, has been amended as follows:

The protein according to the present invention includes proteins in general which have specific physicochemical properties and those derived from natural sources and those prepared by the recombinant DNA technology. The present protein generally has a partially or totally revealed amino acid sequence, for example, the amino acid sequence containing the N-terminal in SEQ ID NO:3 and its homologous amino acid sequences. Variants, which have ~~complementary~~ homologous amino acid sequence to the one in SEQ ID NO:3, can be obtained by replacing one or more amino acids in SEQ ID NO:3 with other amino acids without alternating the inherent biological properties of the present protein. Even when used the same DNA and depending on hosts into which the DNA is introduced, as well as on the components of nutrient culture media, the conditions of cultivation temperature and pH for culturing transformants containing the DNA, it may be formed variants, which are defective in or additionally contain one or more amino acids near to the N-terminal in SEQ ID NO:3 while retaining the inherent biological properties of the protein, by the modification with internal enzymes of the hosts after the DNA expression. The

present protein includes such variants as long as they induce the IFN- $\gamma$  production by immunocompetent cells.

IN THE CLAIMS

1(Once-amended). An IFN- $\gamma$  production inducing agent which ~~contains~~ consists essentially of an effective ingredient capable of inducing IFN- $\gamma$  production by immunocompetent cells, said effective ingredient consisting of a protein ~~obtainable from mouse liver, said protein having a molecular weight of  $19 \pm 5$  kDa as determined by gel filtration or non-reducing SDS-PAGE and a pI of  $4.8 \pm 1.0$  as determined by chromatofocusing, comprising the amino acid sequences set forth as residues 26-43 and 79-103 of SEQ ID NO:2, and being capable of inducing IFN- $\gamma$  production by immunocompetent cells. (IGIF, IL-18) having the following physicochemical properties:~~

(1) Molecular weight

$19,000 \pm 5,000$  daltons on gel filtration and sodium dodecylsulfate polyacrylamide gel electrophoresis (SDS-PAGE);

(2) Isoelectric point (pI)

$4.8 \pm 1.0$  on chromatofocusing;

(3) Biological activity

Inducing the interferon- $\gamma$  production by immunocompetent cells; and

(4) Partial amino acid sequence

Possessing a part or the whole of the amino acid  
sequence of SEQ ID NO:2, wherein Xaa is Met or Thr.

2(Once-amended). A pharmaceutical composition comprising a pharmaceutically-acceptable carrier and an effective ingredient capable of inducing IFN- $\gamma$  production by immunocompetent cells, said effective ingredient consisting of ~~the a protein obtainable from mouse liver, said protein having a molecular weight of  $19 \pm 5$  kDa as determined by gel filtration or non-reducing SDS-PAGE and a pI of  $4.8 \pm 1.0$  as determined by chromatofocusing, comprising the amino acid sequences set forth as residues 26-43 and 79-103 of SEQ ID NO:2, and being capable of inducing IFN- $\gamma$  production by immunocompetent cells.~~ (IGIF, IL-18) having the following physicochemical properties:

(1) Molecular weight

$19,000 \pm 5,000$  daltons on gel filtration and sodium  
dodecylsulfate polyacrylamide gel electrophoresis  
(SDS-PAGE);

(2) Isoelectric point (pI)

$4.8 \pm 1.0$  on chromatofocusing;

(3) Biological activity

Inducing the interferon- $\gamma$  production by  
immunocompetent cells; and

(4) Partial amino acid sequence

Possessing a part or the whole of the amino acid  
sequence of SEQ ID NO:2, wherein Xaa is Met or Thr.

3(Once-amended). A purified protein which is a variant  
of a protein (IGIF, IL-18) having the following physicochemical  
properties:

~~obtained from mouse liver capable of inducing IFN- $\gamma$  production by~~  
~~immunocompetent cells and having an amino acid sequence of SEQ ID~~  
~~NO:2 where residue 70 is methionine or threonine,~~

(1) Molecular weight

19,000 $\pm$ 5,000 daltons on gel filtration and sodium  
dodecylsulfate polyacrylamide gel electrophoresis  
(SDS-PAGE);

(2) Isoelectric point (pI)

4.8  $\pm$  1.0 on chromatofocusing;

(3) Biological activity

Inducing the interferon- $\gamma$  production by  
immunocompetent cells; and

(4) Partial amino acid sequence

Possessing a part or the whole of the amino acid  
sequence of SEQ ID NO:2, wherein Xaa is Met or Thr.

wherein said variant has the amino acid sequence of SEQ ID NO:2  
with at least one ~~or more~~ amino acid residue in SEQ ID NO:2  
replaced with different amino acids, or at least one ~~or more~~ amino  
acid residues deleted or added to the N-terminus of SEQ ID NO:2

~~while not substantially altering the physicochemical properties of the protein retaining the biological property of being capable of inducing IFN- $\gamma$  production by immunocompetent cells.~~

4(Once-amended). The purified protein according to claim 3, wherein said variant has at least one amino acid residue in SEQ ID NO:2 replaced with a different amino acid residue.

5(Once-amended). The purified protein according to claim 3, wherein said variant has at least one ~~or more~~ amino acid residues deleted or added to the N-terminus of SEQ ID NO:2.

6(Once-amended). A pharmaceutical composition comprising a pharmaceutically-acceptable carrier and, as an active ingredient, the protein of claim 53.

7(Once-amended). A purified protein (IGIF, IL-18) which has the amino acid sequence of SEQ ID NO:2, where Xaa represents methionine or threonine.

8(Once-amended). An IFN- $\gamma$  production inducing agent which contains consists essentially of, as an effective ingredient, the protein of claim 7.